

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
15 January 2004 (15.01.2004)

PCT

(10) International Publication Number
WO 2004/005543 A1

- (51) International Patent Classification⁷: **C12Q 1/68**
- (21) International Application Number:
PCT/EP2003/006690
- (22) International Filing Date: 25 June 2003 (25.06.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
102 30 692.3 8 July 2002 (08.07.2002) DE
- (71) Applicant (for all designated States except US): **EPIGENOMICS AG** [DE/DE]; Kastanienallee 24, 10435 Berlin (DE).
- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **HORNS, Torsten** [DE/DE]; Baseler Strasse 162, 12205 Berlin (DE).
- (74) Agents: **KRAUSS, Jan, B. et al.**; Pettenkoferstrasse 20-22, 80336 Munich (DE).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: METHODS AND NUCLEIC ACIDS FOR THE ANALYSIS OF METHYLATION PATTERNS WITHIN THE DD3 GENE

(57) Abstract: The disclosed invention provides methods and sequences for the analysis of methylation patterns within the 5' and promoter regions of the gene DD3.

WO 2004/005543 A1

INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/EP 03/06690

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12Q1/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12Q C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EMBL, EPO-Internal, BIOSIS, EMBASE, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 02 24718 A (ALI SHUJATH ;RECIPON HERVE (US); DIADEXUS INC (US); SUN YONGMING () 28 March 2002 (2002-03-28) page 103, line 7-16 SEQ ID NO. 3 | 1-40 |
| L | & DATABASE EMBL 23 September 2002 (2002-09-23) SUN ET AL.: "Human PSNA cDNA, Pro123". Database accession no. AAD38815 the whole document | 1-40 |
| X | DATABASE EMBL14 June 2000 (2000-06-14) LEONGAMORN LERT D.: "Human DNA sequence from clone RP11-108L4 on chromosome 9" Database accession no. AL359314 XP002254952 Sequence segment 104439-108019 | 1-40 |
| | --- -/-- --- | |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

18 September 2003

Date of mailing of the international search report

30/09/2003.

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Aguilera, M

INTERNATIONAL SEARCH REPORT

nal Application No

PCT/EP 03/06690

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| L | <p>DATABASE EMBL 13 September 2002 (2002-09-13) SCHLEGEL ET AL.: "Human prostate expression marker cDNA 11433" Database accession no. ABV11442 XP002254953 the whole document</p> | 1-40 |
| X | <p>& WO 01 60860 A (MILLENNIUM PREDICTIVE MEDICINE INC.) 23 August 2001 (2001-08-23) page 1863</p> | 1-40 |
| X | <p>WO 97 20924 A (QUADRIFOGLIO FRANCO ; SAICOM S R L (IT); SCAGGIANTE BRUNA (IT)) 12 June 1997 (1997-06-12) page 11; example 4</p> | 1-40 |
| X | <p>WO 98 45420 A (DIAGNOCURE INC ; BUSSEMAKERS MARION J G (NL)) 15 October 1998 (1998-10-15) figure 4; example 3</p> | 1-40 |
| X | <p>& DATABASE EMBL 30 December 1998 (1998-12-30) BUSSEMAKERS MJG: "Prostate cancer antigen PCA3 gene transcription start site" Database accession no. AAV33791 the whole document</p> | 1-40 |
| X | <p>BUSSEMAKERS M J G ET AL: "DD3: NEW PROSTATE-SPECIFIC GENE, HIGHLY OVEREXPRESSED IN PROSTATE CANCER" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 59, 1 December 1999 (1999-12-01), pages 5975-5979, XP002923011 ISSN: 0008-5472 the whole document</p> | 1-40 |
| A | <p>WO 99 55905 A (MOLLOY PETER LAURENCE ; CLARK SUSAN JOY (AU); COMMW SCIENT IND RES) 4 November 1999 (1999-11-04) abstract</p> | |
| A | <p>WO 01 23550 A (FRADET YVES ; BUSSE URSULA (CA); CHYPRE CAMILLE (CA); DIAGNOCURE IN) 5 April 2001 (2001-04-05) abstract</p> | |
| | -/-- | |

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06690

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| A | <p>GITAN RAAD S ET AL: "Methylation-specific oligonucleotide microarray: a new potential for high-throughput methylation analysis"</p> <p>GENOME RESEARCH, COLD SPRING HARBOR LABORATORY PRESS, US, vol. 12, no. 1, January 2002 (2002-01), pages 158-164, XP002208051 ISSN: 1088-9051 the whole document</p> | |
| P,X | <p>JP 2002 360255 A (UNIV HOSPITAL NIJMEGEN) 17 December 2002 (2002-12-17) * page 8 of the english language section of the document *</p> <p>page 8</p> | 1-40 |

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claim 41 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Claims Nos.: 41

Although claim 41 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Claims Nos.: 1-40 (all partially)

In view of the large number of independent claims and also the obscure dependency structure of the claims presently on file, which render it difficult, if not impossible, to determine the matter for which protection is sought, the present application fails to comply with the clarity and conciseness requirements of PCT Article 6 (see also PCT Rule 6.1(a)) to such an extent that a meaningful search on the basis of the claims is impossible.

In addition, claims 9-41 relate to an extremely large number of possible products, and uses of said products. The claims comprise a virtually infinite number of combinations of "at least two oligomers" of "at least 10 nucleotides" from five sequences of 3581 nucleotides each in different configurations and uses. In fact, the claim contains so many options that a lack of conciseness within the meaning of PCT Article 6 arises to such an extent as to render a meaningful search of said claims impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be clear and concise, namely methods for the analysis of cell proliferative disorders comprising the determination of the methylation state of the DD3 promoter region defined by SEQ ID NO.1 to 5, oligonucleotides of at least 10 nucleotides according to sequences SEQ ID NO.1 to 5, and arrays of said oligonucleotides or equivalent oligomers.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

applicant is advised that the EPO policy when acting as IPEA is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/06690

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 41
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 1-40 (all partially)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Patent Application No

PCT/EP 03/06690

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|--|--|
| WO 0224718 | A | 28-03-2002 | AU 9284201 A WO 0224718 A1 US 2003031678 A1 | 02-04-2002 28-03-2002 13-02-2003 |
| WO 0160860 | A | 23-08-2001 | AU 4154101 A WO 0160860 A2 | 27-08-2001 23-08-2001 |
| WO 9720924 | A | 12-06-1997 | IT MI952539 A1 AU 1175497 A WO 9720924 A1 | 04-06-1997 27-06-1997 12-06-1997 |
| WO 9845420 | A | 15-10-1998 | AU 7019498 A WO 9845420 A1 EP 1007650 A1 JP 2001522240 T | 30-10-1998 15-10-1998 14-06-2000 13-11-2001 |
| WO 9955905 | A | 04-11-1999 | AU 3324199 A WO 9955905 A1 CA 2326494 A1 EP 1071815 A1 JP 2002512810 T ZA 200006803 A | 16-11-1999 04-11-1999 04-11-1999 31-01-2001 08-05-2002 10-05-2001 |
| WO 0123550 | A | 05-04-2001 | AU 7636400 A WO 0123550 A2 CA 2385477 A1 EP 1222266 A2 JP 2003510075 T | 30-04-2001 05-04-2001 05-04-2001 17-07-2002 18-03-2003 |
| JP 2002360255 | A | 17-12-2002 | CA 2357073 A1 | 30-11-2002 |